REMARKS

Claims 1-8, 14, 16-63, 69, and 71-80 are pending in this application. Claims 30-55 are withdrawn from consideration. Claims 1-8, 14, 16-23, 25-29, 56-63, 69, and 71-80 were variously rejected under 35 U.S.C. § 112, first paragraph. Claim 25 was rejected under 37 CFR 1.75. Claim 24 was objected to for depending from a rejected base claim.

By this amendment, claim 21 has been canceled and claims 20, 22, 25, and 75 have been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification. The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-8, 14, 16-23, 25-29, 56-63, 69, and 71-80 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claims 1-8, 14, 16-23, 25-29, 56-63, 69, and 71-80 were rejected under 35 U.S.C. §112, first paragraph, for allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. Applicants respectfully traverse these rejections.

Written Description

The written description requirement "may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure" and compliance with the requirement "is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" See *Amgen, Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.*, 65 USPQ2d 1385 (Fed. Cir. 2003); *Enzo Biochem, Inc. v Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002).

The claimed invention is directed to an immunomodulatory polynucleotide/microcarrier (IMP/MC) complex comprising a polynucleotide linked to a nonbiodegradable microcarrier. The polynucleotide component of the claimed IMP/MC complex is the focus of this written description rejection. The Examiner asserts that "the specification and claims do not indicate what distinguishing attributes are shared by the members of the genus" and an "ISS oligonucleotides sequence identified in the claims" alone is insufficient to describe the genus." Office Action, page 4. In support of this rejection, Van Uden,[1], Fearon,[2] and *The Regents of the University of California v. Eli Lilly*, 43 USPQ2d 1398-1412 (Fed. Cir. 1997; hereinafter "*Eli Lilly*") are cited.

With regard to claims 1 and 56, Applicants respectfully submit that distinguishing attributes shared by the members of the claimed ISS genus is a length of 7 to about 200 nucleotides and a 5'-TCGXXXX sequence, and the claimed genus includes a sequence selected from 5'-TCGAAAA, 5'-TCGCCCC, 5'-TCGGGGG, 5'-TCGTTTT, and 5'-TCGTCGX. With regard to claim 20, distinguishing attributes shared by the members of the claimed polynucleotide genus is a length of 7 nucleotides including a CG dinucleotide sequence. Applicants submit that a distinguishing attribute shared by members of the claimed genus is clear and the pending claims are fully described in the specification as filed. Solely in the interest of expediting prosecution of the instant application, claim 20 has herein been amended to be directed to a complex wherein the polynucleotide comprises the sequence TCG.

[1] Van Uden et al. (1999, *J. Allergy Clin. Immunol.* 104:902-910, "Van Uden"), of record.
[2] Fearon et al. (2003, Eur. J. Immunol. 33:3114-2122, "Fearon"), of record.

The Van Uden and Fearon references do not support this written description rejection. Van Uden, published well before the filing date of the present application, describes a variety of immunostimulatory DNA sequences. Van Uden does not mention the claimed sequences or polynucleotides comprising the claimed sequences. Thus, comments in Van Uden about sequence structure required for immunostimulation are not directed to, nor relevant to, the claimed sequences. Fearon reports that the studies described therein "define a minimal ISS motif for the optimal induction of IFN-γ and IFN-α from human PBMC to be 5'-TCGXX-3', where X can be any nucleotide."[3] All of the ISS in the claimed invention include this minimal sequence. Thus, the studies reported in Fearon confirm the teaching of the present invention and nothing in Fearon contradicts the claimed invention.

The Examiner states that Fearon et al. "set forth that "flanking sequences" of ISS molecules can have "confounding effects." (See page 2115)." This statement takes Fearon's comment out of context and is misleading as to the discussion in Fearon. On page 2115,[4] Fearon states that "[t]hese observations suggested a strategy for determining the optimum size, sequence, and position of the immunostimulatory motif without the confounding effects of flanking sequences that may be needed for cellular uptake or stability, but not for TLR9-mediated activiation." Emphasis added. Fearon is referring to a formulation strategy for studying the immunostimulatory activity of oligonucleotides containing less than 8 nucleotides without having to account for effects that flanking sequences may have on cellular uptake or stability of the oligonucleotide.[5] The "confounding effects of flanking sequences" does not refer to effects on immunostimulatory activity. Thus, this document in no way supports this lack of written description rejection.

Applicants submit that the written description standard used by the Examiner for this rejection is not appropriate for the nature of the present invention. The *Eli Lilly* case is directed to nucleic acid sequences which encode specific polypeptides and, thus, sequences encoding the functional polypeptide were required for written description of the invention. This is indicated by

[3] See, Fearon, page 2120, last paragraph of section 3.
[4] See, Fearon, page 2115, end of the first paragraph of section 2.2.
[5] See, Fearon, page 2115, end of the last paragraph of section 1.

the complete sentence of the section quoted by the Examiner. At section B(1), the court in *Eli Lilly* states: "An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, *Supra*, emphasis added. The subject matter and facts of this case render this decision is not applicable to the facts of the present invention.

Quoting from the Office's Written Description Requirement Guidelines, the court in *Enzo* stated that "the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106 (emphasis added)." *Enzo Biochem, Inc. v Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002).

Claim 20 of the present invention involves a polynucleotide 7 nucleotides in length including the sequence TCG. Thus, any polynucleotide of claim 20 can vary at only four base positions. Claims 1 and 56 of the present invention involves an ISS containing polynucleotide, 7 to about 200 nucleotides in length, where the ISS is selected from 5'-TCGAAAA, 5'-TCGCCCC, 5'-TCGGGGG, 5'-TCGTTTT, and 5'-TCGTCGX. Sequences in addition to the 5'-TCG-3' sequence or the 5'-TCGXXXX sequences claimed known to provide immunostimulatory activity to the oligonucleotide are described in the specification and are known to those of skill in the art, as discussed herein.

Applicants respectfully submit that the specification in combination with that known in the art provides a description of sufficient, relevant, identifying structural and functional characteristics of an immunostimulatory oligonucleotide to adequately describe possession of the claimed genus to one skilled in the art. Thus, the pending claims are fully described in the specification as filed. Accordingly, Applicants respectfully submit that the written description requirement has been met.

Enablement

The polynucleotide component of the claimed IMP/MC complex is the focus of this enablement rejection. The Examiner states that "one of skill in the art would be forced into excessive experimentation to practice the broadly claimed invention." Office Action, page 7. Applicants respectfully disagree with this assessment of the teaching of the specification and the knowledge in the art.

The polynucleotide component of the claimed IMP/MC complex is described in the specification, for example, at pages 19-25. Further, the specification describes indications and assays by which the immunostimulatory activity of a particular IMP/MC complex can be assessed. See, for example, specification pages 54-55 and 60-62. Immunostimulatory oligonucleotides comprising a 5'-CG-3' sequence were also well known in the art at the time the present application was filed. References listed on pages 4 and 5 of the specification and submitted to the Office on November 13, 2001 describe many immunostimulatory oligonucleotides comprising a 5'-CG-3' sequence, assays by which the immunostimulatory activity is assessed and cite further references describing additional immunostimulatory oligonucleotides. Applicants submit that immunostimulatory oligonucleotides are well known in the art and that the ISS art is more mature than the Examiner asserts.

The Examiner supports this enablement rejection by citing the Van Uden and Fearon references. These references are discussed above and Applicants submit that they do not support a state of the art such that the claimed invention is not enabled. Van Uden does not mention the claimed sequences or polynucleotides comprising the claimed sequences. Thus, comments in Van Uden about fundamental aspects of ISS are not directed to, nor relevant to, the claimed sequences. The appropriate context in Fearon of the phrase "confounding effects" is discussed above and this phrase does not refer to effects on immunostimulatory activity. In fact, the claimed polynucleotides all comprise the sequence TCG, which Fearon reports as a minimal notif for optimal induction of

IFN-γ and IFN-α from human PBMC.[6] Thus, the teachings of Fearon only serve to support that the claimed invention is enabled by the specification.

Fulfillment of the enablement requirement does not require that every embodiment of the invention be predictable. Rather, unpredictability is permitted, the level of unpredictability permitted depending on the level of guidance provided by the specification and the knowledge in the art. Applicants respectfully note that the test for enablement is not whether a certain amount of experimentation is required to practice an invention, but rather whether the amount of experimentation is "undue." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). "Since one embodiment is ... disclosed in the specification, along with the general manner in which its current range was ascertained, ... other permutations of the invention could be practiced by those skilled in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d. 788, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). Applicants respectfully submit that the specification provides a reasonable amount of guidance to the skilled artisan with respect to the direction in which the experimentation should proceed to optimize the teachings of the specification and the art and that any additional necessary experimentation is presumed to be within the level of ordinary skill in the art.

According to the Office, claims are not rejected as broader than the enabling disclosure under 35 U.S.C. §112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider obvious. MPEP §2164.08. The court has stated that "Enablement is not precluded by the necessity for some experimentation such as routine screening ...". *In re Wands*, *Supra*. Applicants respectfully submit that varying the nucleic acid sequence of oligonucleotides and testing the oligonucleotides for immunostimulatory activity are well within the bounds of routine experimentation by one of skill in the art.

[6] See, Fearon, page 2120, last paragraph of section 3.

In addition, the Office has issued claims directed to methods of treating a mammal, a subject or an individual through administering an immunostimulatory or immunomodulatory polynucleotide comprising an ISS, wherein the ISS comprises the sequence 5'-CG-3'.[7] One of these patents, U.S. Pat. No. 6,498,148, has a claimed priority date years before than the priority date of the instant application and the others have claimed priority dates within a few months of the priority date of the instant application. Although the claims in these patents are supported with experiments in which a limited number of 5'-CG-3' containing oligonucleotides were tested for a particular activity or effect in a mouse model and, in some cases, on human cells in culture, the Office has apparently deemed the state of the art such that the task of identifying nucleotides surrounding the core 5'-CG-3' motif as not an undue burden to the skilled artisan.

Thus, Applicants respectfully submit that the pending claims are in compliance with the enablement requirements and a *prima facie* case of lack of enablement has not been established.

In sum, Applicants submit that the pending claims fall within the subject matter that is described and enabled by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejection Under 37 CFR 1.75

Claim 25 was rejected under 37 CFR §1.75 as allegedly being a substantial duplicate of claim 21. Applicants respectfully traverse this rejection. Although Applicants believe that the claims were not duplicates when considered in view of the specification and the understanding of those of skill in the art, Applicants have attempted to respond to the concern of the Examiner with the amendment of claim 25 in order to facilitate disposition of the present case. Accordingly, Applicants respectfully request withdrawal of the double patenting rejection.

[7] See, for example, U.S. Pat. Nos. 6,613,751, 6,552,006, 6,534,062 and 6,498,148.

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001720. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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